REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. In particular, claims 1, 11, 124, 125, 126, 127, 157, 158, 160, and 161-163 are amended by way of this communication. None of the amendments raise any issue of new matter.

After amending the claims set forth above, claims 1, 11, 24 and 124-169 are currently pending in the instant application. All claim amendments find support in the application specification and in the claims as originally filed.

Objection to the Disclosure

Applicant respectfully submits that the amendments to the specification in the instant communication obviate the Examiner's objection to the disclosure.

Rejection of claims 1, 11, and 124-163 under 35 U.S.C. § 112, second paragraph

The rejection of claims 1, 11, and 124-163 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite is respectfully traversed.

Applicants respectfully submit that one of ordinary skill would understand the metes and bounds of the scope of the claim using the "at least about" language. The rejection itself states that the use of the term "about" is indefinite **"where there was close prior art."** As discussed below, there is no such "close prior art;" thus, the basis for the rejection fails. However, in order to reduce the issues and advance prosecution the claims as amended no longer recite the term "at least about." Accordingly, the rejection has been rendered moot.

Rejection of Claims 1, 11, 124-128, 130, 131, 137, 138, 141-148, 151, 152, 156-159, 166, and 168 Under 35 U.S.C. § 102(b) over Nakai as evidenced by Biswas et al.

The rejection of claims 1, 11, 124-128, 130, 131, 137, 138, 141-148, 151, 152, 156-159, 166, and 168 under 35 U.S.C. §102(b) as allegedly being anticipated by Nakai (The Journal of Biological Chemistry (1993) 268(32):23997-24004; hereinafter "Nakai") as evidenced by Biswas et al. (Biochemical Journal (2004) 379(Pt 3):553-562; hereinafter "Biswas") is respectfully traversed.

The Examiner appears to have misunderstood the Nakai reference. The Nakai reference discloses replication of DNA and does not disclose a method of amplifying a template DNA molecule meeting the elements of the instant claims.

For example, contrary to the Examiner's assertion, Nakai does not disclose a method performed under conditions such that the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture. Specifically, Table 1 on page 23998 discloses the amount of DNA replicated in the *in vivo* reaction. As can be seen on the table, 376 pmol was added to the reaction—the largest yield of replicated DNA was only 63.5 pmol. Thus, the replicated DNA in the largest yielding reaction represents a small fraction (~17%) of the DNA put into the reaction—nothing near the 10-fold increase required by the claims. At page 5 of the office action the Examiner points to page 24003, column one to assert that the Nakai discloses a "10-fold amplification." Contrary to the Examiner's Assertion, the term "10-fold" cited on page 24003 refers to the fact that one of the products of the replication reaction (mini-Mu sequences) was produced in quantities that are 10-fold higher than a second product (vector sequences). The "10-fold" mentioned in Nakai does not refer to the amount of amplified product with respect to the amount of template DNA put into the reaction mixture (to the contrary on Table 1 Nikai discloses that the amount of amplified DNA is actually less than the amount of DNA put into the reaction). Accordingly, Nikai does not disclose a method performed under

conditions such that the amount of amplified product is at least 10-fold greater than the amount of template DNA put into the mixture as required by the claims.

The Examiner also erroneously alleges that the amplification of Nakai is "exponential." The instant specification defines exponential at page 5, line 25 to page 6, line 2 as "[b]y exponential it is meant that at some period of time during the reaction the rate of DNA synthesis increases. In other words, the amount of DNA synthesized at a particular time will be greater than twice the amount of DNA synthesized at half the time. For example, if the amount of DNA synthesized after 20 minutes is ten times the amount of DNA synthesized after 10 minutes, then the kinetics of DNA synthesis is exponential. On the other hand, if the amount of DNA synthesized after 20 minutes is only twice the amount of DNA synthesized after 10 minutes, then the kinetics of DNA synthesis is linear." Nakai fails to provide any information regarding the rate of DNA synthesis over time, thus, the reference cannot anticipate a method resulting in exponential amplification as recited in the claims. Moreover, given the very low amounts of DNA synthesized by the Nakai reactions, one of ordinary skill would conclude that the amplification is not exponential in accordance with the claimed methods.

The Examiner further alleges that "Nakai teaches that the accessory protein is a helicase or a primase" citing to Nakai at page 23997, column 2 and page 23998, column 1 as alleged support. Also citing to Nakai at page 23997 at column 2, and at page 2398, the examiner alleges that Nakai discloses that the reaction includes DnaC protein (a protein that binds single-stranded DNA); amplification at 37°C; and a reaction mixture that comprises an ATP regeneration system that comprises phosphoreatine and creatine kinase. The replication reactions described in these excerpts (i.e., page 23997 and 23998) are the reactions with results shown on Table 1 that yielded product DNA that was at most only 17% of the amount of DNA put into the reactions. This yield falls well short of the claimed methods that yield an amount of amplification product that is at least 10-fold greater (or 100-fold greater; or 1,000 fold greater; or 1,000,000 greater) than the amount of DNA put into the reaction. Accordingly, these disclosures fall well short of anticipating the instant claims.

The Examiner further alleges that Nakai teaches replication using T7 DNA polymerase at page 24002 and Figure 7. The Examiner also cites to page 24002 and Figure 7 to allege disclosure of a reaction that includes a single-stranded DNA binding protein and a reaction at 37°C. The reactions disclosed on the right hand column of page 24002 and figure 7 of Nakai were performed to characterize the high molecular weight products of other reactions. See last full paragraph of the left hand column on page 24002 and discussion of results on pages 24002-24003. There is no indication of the amount of DNA produced by the reaction, much less that the amount of amplified products is at least 10-fold greater (or 100-fold greater; or 1,000 fold greater; or 1,000,000 greater) than the amount of template DNA put into the mixture as recited in the claims. To the contrary, one of ordinary skill would conclude that the Nakai reaction disclosed on page 24002 would not to yield the levels of amplification disclosed in the instant application without primers because the Nakai reaction uses the **small** form of T7 gene four protein (i.e., the 56 kDa form) that does not have primase activity. See Nakai at page 24002, right hand column, lines 4-5; *See also* Application at page 14, lines 11-14 indicating that efficient amplification according to the disclosed methods requires the large 63 kDa form having primase activity. As such, the reaction on page on page 24002 and in figure 7 Nakai would result replication that is linear in nature (as opposed to exponential) and would yield much lower amounts of DNA than the amplification reactions as defined by the instant claims. Accordingly the reactions disclosed on page 24002 and in figure 7 of Nakai fail to anticipate the instantly claimed methods.

Accordingly, reconsideration and withdrawal of the section 102 rejections are respectfully requested.

Rejection of Claims 24, 160-164, and 169 Under 35 U.S.C. § 103(a) over Nakai as evidenced by Biswas in view of Tabor et al. and further in view of Bernstein et al. and further in view of Tabor et al.

The rejection of claims 24, 160-164, and 169 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas, in view of Tabor et al. (The Journal of Biological Chemistry (1989) 264(11): 6447-6458; cited on IDS; hereinafter "Tabor I") and further in view of Bernstein et al. (Proceedings of the National Academy of Sciences, USA (1998) 85:396-400; cited on IDS) and further in view of Tabor et al. (Journal of Biological Chemistry (1987) 262(33): 16212-16223; cited on IDS; hereinafter "Tabor II") is respectfully traversed.

In order to make a *prima facie* case of obviousness, the Examiner must demonstrate that the prior art (i) teaches or suggests every claim limitation, (ii) provides a motivation to combine (or modify) the teachings of the selected references, and (iii) provides a reasonable expectation of success. In re Vaeck, 947 F.3d 488, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP § 2143. This is the "TSM" test for obviousness which was recently affirmed by the Supreme Court. KSR Int'l Co. v. Teleflex Inc., No. 04-1350, 550 U.S. ____, slip op. at 15 (2007). In explicating the correct standard for this test, the KSR Court reaffirmed previous holdings that an invention "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id at 14, see also, In re Rouffet, 149 F.3d 1350, 1357, 47 USPQ2d 1453 (Fed. Cir. 1998). Furthermore, the Court warned the fact finder to be aware of the distortion caused by hindsight bias and to be cautious of arguments reliant upon *ex post* reasoning. KSR, slip op. at 17.

The inventions encompassed by the instant claims are based, at least in part, on the surprising discovery that incubating template DNA with reaction mixtures specified in the instant claims under the proper conditions results in an unexpectedly large amount of DNA synthesis. Nakai is exemplary of prior art replication reactions that fall well short of the claimed methods capable of yielding an amount of amplification product that is at least 10-fold greater (or 100-

fold greater; or 1,000 fold greater; or 1,000,000 greater) than the amount of DNA put into the reaction and that amplify DNA exponentially. As such, without the benefit of hindsight provided by the teaching of the instant application, one of ordinary skill would have had no reasonable expectation that such methods as instantly claimed would work to generate the amounts of amplified product disclosed in the application and recited in the claims.

Claim 24 and 169, and the claims dependent thereon, specifically recite that the reaction mixtures include the 63-kDa form of the gene 4 protein from bacteriophage T7 with specific other ingredients including a wild-type T7 DNA polymerase and a T7 DNA polymerase modified to have reduced 3'-5' exonuclease activity. The application discusses the advantages of the 63 kDa form of T7 gene 4 protein in the inventive amplification methods, for example at page 14, lines 11-14. To the contrary the Nakai reaction on page 24003 and figure 7 specifically discloses the use of the **small** form of the T7 gene 4 protein (i.e., the 56 kDa form that does not have primase activity). The specific recitation in Nakai of the small form of T7 gene 4 protein alone would motivate one of ordinary skill against using the 63 kDa form. Moreover, the purpose of the replication reaction described in Nakai at page 24002 were performed to characterize the high molecular weight products of other reactions (for example, to determine whether the products are concatemers or catenanes). See last full paragraph of the left hand column on page 24002 and discussion of results on pages 24002-24003. One of ordinary skill would expect that using the large form of the of T7 gene 4 protein having primase activity would result in priming in the reaction that could preclude the purpose of the Nakai reaction of characterizing the products. Accordingly, the obviousness rejections over claims 24 and 169 fail outright because one would be motivated **against** modifying the primary Nakai reaction to the 63 kDa form of the T7 gene 4 protein because using that form of the T7 gene product would defeat the purpose of reaction recited in Nakai.

The rejection of claim 24 and 169 and claims dependent thereon, also fails because the Examiner has provided no motivation for one of ordinary skill to combine the specific ingredients recited in the claim to arrive at the claimed method. For Example, the neither the

Examiner, the cited references nor the art in general provides any motivation to include both a wild-type T7 DNA polymerase **and** a T7 DNA polymerase modified to have reduced 3'-5' exonuclease activity in the same amplification reaction without exogenously added primers as recited in claim 24, much less specific combination of the two forms of T7 polymerase with the 63 kDa form of the T7 gene 4 protein as claimed. The Examiner's assertion that the instantly claimed methods could be achieved by non-inventive "routine optimization" is unavailing because none of the references disclose any amplification methods that achieve yields of amplified DNA products even close to that disclosed in the instant invention and because the each of the replication reactions disclosed in the prior art were not performed for the purpose of amplifying large amounts of DNA, but rather were for other purposes (such as characterizing products as in Nakai) or as academic reports of natural DNA replication systems. As such, the obviousness rejections are a classic case of hindsight bias where the Examiner has simply decomposed the claimed invention into its constituent elements, located the elements in the prior art and then asserted that it is obvious to reassemble these elements in the specific combination to arrive at the claimed invention—the exact type of hindsight bias that the Supreme Court warned against in KSR. KSR, slip op. at 17.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 24, 160-164, and 169 are respectfully requested.

Rejection of Claims 124-127, 157, and 158 Under 35 U.S.C. § 103(a) over Nakai as evidenced by Biswas

The rejection of claims 124-127, 157, and 158 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas is respectfully traversed.

As discussed above, prior to the disclosures provided by the instant application, one of ordinary skill would have had no reasonable expectation that the specific combinations of ingredients for amplification reaction mixtures recited in the claims could be capable of yielding

an amount of amplification product that is at least 10-fold greater (or 100-fold greater; or 1,000 fold greater; or 1,000,000 greater) than the amount of DNA put into the reaction, or that amplify target DNA exponentially as the instant claims require. The Nakai reference directly supports this concept because the greatest yields for a replication reaction reported in Nakai are mere fraction of the DNA put into the reaction. That is, the most efficient results reported for a Nakai replication is ~17% of the DNA put into the reaction (i.e., the product DNA is **less** than the DNA put into the reaction); a result that is typical of prior art replication reactions. Thus, for the reasons described above and because the Nakai replication reactions fall so far short of the instant claims, there would be no motivation to modify Nakai to arrive at the instantly claimed methods nor would there be any reasonable expectation that the methods as claimed would work.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 124-127, 157, and 158 are respectfully requested.

Rejection of Claims 129, 132-136, and 165 Under 35 U.S.C. § 103(a) over Nakai as evidenced by Biswas in view of Tabor I

The rejection of claims 129, 132-136, and 165 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas in view of Tabor I is respectfully traversed.

In this rejection, the Examiner admits that Nakai fails to teach any reaction having two forms of T7 DNA polymerase as required in the instant claims; and therefore relies on Tabor I to assert that it would be obvious to modify Nakai to arrive at the instantly claimed invention.

Applicant respectfully submits that the obviousness rejection fails because there would be no motivation for one of ordinary skill to combine Tabor I with the methods of Nakai and even if there was such motivation, there would be no reasonable expectation that the methods as claimed would work.

With respect to motivation the examiner admits that Tabor I states that the modified form of T7 that has reduced DNA polymerase activity is useful for DNA sequence analysis. To the contrary, the reactions of Nakai have nothing to do with analyzing any nucleic acid sequence, therefore there would be no reason for one of ordinary skill to include a form of T7 modified to have reduced 3'-5' exonuclease activity in the Nikai reactions. Even if there were motivation to replace the unmodified T7 polymerase with a modified T7 polymerase disclosed in Tabor I (there isn't), without the benefit of hindsight of the instant application there still would be no motivation to use both an unmodified form of T7 **and** a form of T7 polymerase modified to have reduced 3'-5' exonuclease activity in the same reaction as recited in the claims.

Finally, even if one did modify the methods of Nakai to use two both forms of T7 polymerase in the replication reaction; as discussed above there would be no reasonable expectation that the methods would result in the yields of amplified products recited in the claims.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 129, 132-136, and 165 are respectfully requested.

Rejection of Claims 129, 132-136, 139, 140 and 165 Under 35 U.S.C. § 103(a)

The rejections of claims 129, 132-136, and 165 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas in view of Tabor I and the rejection of claims 139 and 140 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas in view of Bernstein are respectfully traversed.

In these rejections, the Examiner admits that Nakai discloses the use of the 56 kDa form of the T7 gene 4 product rather than the 63 kDa form recited in the claims; and alleges that it would be obvious to replace the small form of the gene 4 product of the Nakai method because "an ordinary practitioner would have been motivated by these teachings of Bernsten to substitute the 63 kDa form of the T7 gene protein for the 56 kDa form taught by Nakai, in order to obtain

the primase activity required for lagging strand synthesis." The Examiner fails to explain, however, why one of ordinary skill would be motivated to have lagging strand synthesis in the Nakai replication reaction. To the contrary, Applicant respectfully submits that the small form of T7 gene four product was particularly well suited for the purposes of characterizing DNA products as Nakai explained the reactions were used for; and, as described above, that one of ordinary skill would appreciate that substituting the large form of the T7 gene product could interfere with this purpose of the reaction (for example, by lagging strand synthesis). Accordingly, one of ordinary skill would be motivated **against** making the combination suggested by the Examiner.

Moreover, as discussed above, the rejection also fails because one of ordinary skill would have no reasonable expectation that the methods could successfully be performed such that the amount of amplified products is at least 10-fold greater than the amount of template DNA put into the mixture as the claims require.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 129, 129, 132-136, 139, 140 and 165 are respectfully requested.

Rejection of Claim 149, 150 and 155 Under 35 U.S.C. § 103(a)

The rejection of claim 149 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas in view of Tabor I; the rejection of claim 150 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas in view of Peller (Biochemistry (1977) 16(3): 387-395; hereinafter "Peller"); and 155 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas in view of Jarvis et al. (The Journal of Biological Chemistry (1990) 265(25): 15160-15167; hereinafter Jarvis) are respectfully traversed.

For at least the reasons discussed above, the Examiner has failed to establish any *prima facie* novelty or obviousness rejection for claim 1 (the claim from which claims 149, 150 and 150 depend), much less any obviousness rejection for the additional elements recited in the dependant claims. None of the references cited in these rejections, alone or in any combination cure the deficiencies described above; thus no *prima facie* obviousness rejections have been established for claims 149, 150 and 155.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 149, 150 and 155 are respectfully requested.

Rejection of Claims 153 and 154 Under 35 U.S.C. § 103(a) over Nakai as evidenced by Biswas in view of Engler et al.

The rejection of claims 153 and 154 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas in view of Engler et al. (The Journal of Biological Chemistry (1983) 258(18): 11197-11205; hereinafter "Engler") is respectfully traversed.

In these rejections, the Examiner admits that Nakai fails to disclose any method in which ligase is added to the reaction mixture; and alleges that it would be obvious to add ligase to the Nakai reactions based on the disclosures of Englar.

Applicant respectfully submits that for at least the reasons discussed above, the Examiner has failed to establish any *prima facie* novelty or obviousness rejection for claim 1, the claim from which claims 153 and 154 depend. None of the references cited in this rejections, alone or in any combination cure the deficiencies described above thus no *prima facie* obviousness rejections have been established for claims 153 and 154.

However, applicants respectfully submit that there would be no motivation to combine the ligase of Engler in the Nakai reactions. As with the large form of the T7 gene four product, the Examiner bases the alleged motivation on the allegation one of ordinary skill would be

motivated to modify the methods of Nakai such to have successful lagging strand synthesis. As described above, lagging strand synthesis is not required to achieve the goals of the Nakai reactions (i.e., the characterization of the DNA products), and would likely rather interfere with the ability to characterize the products as reported in the right hand column of 24002 to the left hand column of page 24003. Accordingly, one of ordinary skill would be motivated against combining the ligase of Engler in the Nakai reactions.

Moreover, as discussed above, the rejection also fails because one of ordinary skill would have no reasonable expectation that the methods could successfully be performed such that the amount of amplified products is at least 10-fold greater than the amount of template DNA put into the mixture as the claims require.

Accordingly, reconsideration and withdrawal of the section 103 rejections of claims 153 and 154 are respectfully requested.

Rejection of Claim 167 Under 35 U.S.C. § 103(a) over Nakai as evidenced by Biswas in view of Tabor I and further in view of Bernstein

The rejection of claim 167 under 35 U.S.C. §103(a) as allegedly being unpatentable over Nakai, as evidenced by Biswas in view of Tabor I and further in view of Bernstein is respectfully traversed.

This rejection, like the rejection of claims 24, 160-164, and 169 discussed above, is based on the allegation that it would be obvious to modify the replication reaction of Nakai to include the 63-kDa form of T7 gene 4 product having primase activity rather than the small form not having primase activity. This rejection fails at least for the same reasons described above with respect to the rejection of claims 24, 160-164, and 169.

Accordingly, reconsideration and withdrawal of the section 103 rejection of claim 167 is respectfully requested.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date: September 21, 2007

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